REMARKS

Claim Objections

4. Claim 1 is objected to because of the following informalities:

- a comma should be inserted between the terms "conjugated lipids" and "prion" in line 4 of the claim; and
- a comma should be inserted between the terms "prion" and "and microbial protein targets" in line 9 of the claim.

Appropriate correction is required.

Response: Appropriate corrections have been made in the amended claim.

Claim Rejections – 35 USC § 112

7. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 provides for a method for the capture of a biological analyte onto a substrate, but, since the claim does not set forth any steps involved in the method/process, it is unclear that method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how the use is actually practiced.

Claim 1 is also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in a process, results in an improper definition of a proecess, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example Ex parte Dunki, 153 USPQ 678 (Bd.App. 1967) and Clinical Products, Ltd. v. Brenner, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)

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Response: Claim 1 has been amended to set forth the steps involved in the method. This amendment also attempts to comply with 35 U.S.C. 112 and 101 by delimiting how the method is practiced. The preamble of the claim now reads, "A method for capture of a biological analyte from a solution onto a substrate whereby the sample is passed over a substrate surface that has been conjugated with non-antibody ligands by photostable tethers wherein:"

8. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim provides for a method of capturing a biological analyte onto a substrate. However, subparts (e) – (k) of the claim each provide for an alternative intended use for the claimed method. It is unclear if the Applicant intended that the claim method requires each of the different embodiments indicated by these subparts to the claim, or if the Applicant intended that these be alternative embodiments. Clarification is required.

Response: Claim 1 has been amended to so that subparts (e) – (f) refer to the preamble of the claim.

9. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the following limitation: "the ligands used" in line 2 of the claims. There is insufficient antecedent basis for this limitation in the claim.

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Response: Claim 1 has been amended so that the limitation "the ligands used" refer to the preamble of the claim.

10. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads on methods for the capture of virus to a substrate using a liquid that may be a "peptide specific for outer membrane proteins." It is noted that the application does not appear to provide any limitation on what form such peptides may take. However, the application does indicate that the "present invention describes the capture of microorganisms and their proteinaceous toxins using non-antibody based ligands." It is therefore unclear whether the claims are intended to be limited to such "non-antibody based ligands," of if the claims are intended to include such antibody based ligands as potential peptides specific for the outer membrane proteins.

For the purposes of this action, because the claims do not appear to be limited to non-antibody based ligands," the claims are read as including the use of antibody-based ligands.

Response: The amendment to Claim 1 now reads, "A method for capture of a biological analyte from a solution onto a substrate whereby the sample is passed over a substrate surface that has been conjugated with non-antibody ligands by photostable tethers wherein:"

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12. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim was amended in a preliminary amendment filed on November 12, 2003 such that the claim now reads on subject matter that is not supported in the application as filed. I.e., the claim has been amended to read on the following embodiments of the claimed inventions which are not supported by the application as filed:

- embodiments wherein the ligand used in the method, or the analyte as detected, is a prion;
- embodiments wherein the substrate is used for the concentration of the analytes from veterinary samples, an aerosol, food product slurries, food ingredient slurries, and soil slurries.

It is noted that the preliminary amendment was filed with the application. However, the application was filed as a division of prior art application 09/999,159 (which does not provide support for the newly added subject matter), along with a copy of the oath/declaration from the parent. Although amended rule 37 CFR 1.115 indicates that, in applications filed on or after September 21, 2004, a supplemental oath or declaration may be filed to account for preliminary amendments filed with the application, such is not the case in applications, such as the present application, that were filed prior to September 21, 2004. See, 69 (182) Federal Register 56518 (left column, first full paragraph). The

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subject matter added by the preliminary amendment of November 12, 2003 is therefore considered New Matter to the application.

Response: The embodiments wherein the substrate is used for concentration of the analytes from veterinary samples, an aerosol, food product slurries, food ingredient slurries and soil slurries, which the examiner has identified as New Matter, have been withdrawn. However, it is well known to those skilled in the art that prions are proteinaceous matter (see, for example, Safar, et al "Measuring prions causing bovine spongiform encephalopathy or chronic wasting disease by immunoassays and transgenic mice" *Nature Biotechnology*, **2002**, 20:1147-1150), and that proteinaceous material is described as a biological analyte in the specification (see pg. 7, line 7 or pg. 12, line 10 of the present application). Since prions are proteinaceous material (with toxic effects) and since proteinaceous material is described in the specification, prions are not New Material.

Claim Rejections – 35 USC § 103

13. ...35 U.S.C. 103(a) ... forms the basis for all obviousness rejections set forth in this Office action: [these rejections follow].

1. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over PCT publication WO 98/495557, naming Powers et al. as inventors. The rejected claim reads on a method capturing a virus to a substrate surface with a ligand, wherein the ligand is specific to an outer membrane protein.

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Powers et al teaches a method of detecting analytes in a sample by contacting the sample to a series of ligands tethered to a surface. Among the ligands taught by the reference are those that bind to proteins of the outer membrane of microbial cells. See, pages 6-11. The reference also teaches that the analyte to be detected may be a virus. See e.g., claim 11. Thus, the reference renders the use of such ligands for the use of capturing a virus to a surface. Although the present application identifies preferred tether lengths for tethers linking the ligand to the substrate, such limitations are obvious as one skilled in the art would know to maximize the effectiveness of such an assay by adjusting the length of the tether to account for the size of the target analyte. See e.g. U.S. Patent 6,124,102, column 18, lines 19-64 (cited in the IDS filed November 12, 2003).

2. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klempner et al. (U.S. Patent Application Publication U.S. 2002/0187464). The rejected claims read on a method for capture of a virus to a substrate using a peptide ligand specific to outer membrane proteins thereof.

Klempner teaches the use of affinity ligand reagents (ALRs) for the detection of biological constructs. See e.g. page 1, paragraph 006; page 2, paragraph 0016; and page 3, paragraph 0022. This reference discloses ALRs as being antibodies, small organic molecules, or polypeptides, and at least 10 different ALRs specific for each analyte to be detected. Page 2, paragraph 0017. Klempner also teaches that the disclosed method may be used as a method that "fingerprints" microorganisms through identification of the molecules on their outer surfaces. Page 7, paragraph 0066. See also, Wang et al., U.S. 5,922,617 (indicating in column 7, lines 53-59, that those skilled in the art would have recognized ALRs that bind to virus surface membrane proteins as obvious embodiments).

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Thus, the reference renders obvious the use of peptides that binds to the outer membrane proteins of the microorganism to be detected. Finally, the reference teaches that among the biological constructs that can be detected by the method taught by Klempner are viruses. Page 1, paragraph 0006. Because the reference teaches that the described ALRs may be used to bind the target virus to the substrate, the reference renders obvious the capture of the virus onto a substrate.

Klempner further teaches that the ALRs may be covalently or non-covalently attached to a substrate surface. Page 6, paragraph 0050. Thus it would have been obvious to one of ordinary skill in the art to covalently attach ligands used in the assay to the surface. Although the present application identifies preferred lengths for linkers (tethers) joining the ligand to the substrate, such limitations are obvious as one skilled in the art would know to maximize the effectiveness of such an assay by adjusting the length of the tether to account for the size of the target analyte. See e.g. U.S. Patent 6,124,102, column 18, lines 19-64. Because the reference teaches the claimed methods, and used the claimed materials to perform the same function, the methods disclosed therein render obvious the invention as described by the identified claims.

Response: As pointed out by the examiner, Powers *et al.* (PCT Publication WO 98/49557) does not teach the indicated tether lengths that are to be used for each analyte to be captured. Powers et al. also doesn't teach the steps of separating the substrate surface from the solution nor washing away non-bound portions of the sample (biological components of the matrix from which the analyte was captured). U. S. Patent 6,124,102 (Fodor, *et al.*) is cited against the claims for being obvious as this invention teaches one to vary linker lengths to

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optimize binding. Fodor, *et al.* teaches the use of their VLSIPS (very large scale immobilized polymer synthesis) methodology to determine receptor-ligand binding between peptides and nucleotides (the ligand-receptor pair covered in their claims). In the disclosure by Fodor, *et al.* the length of the linker is varied to optimize the interaction between an immobilized ligand and its receptor using the VLSIPS methodology (employing a binary synthesis strategy with light-directed chemical synthesis allowing controlled numbers of monomers to be polymerized in a specific position to vary linker length) and that optimal linker length is used to assay other ligands in accordance with their interrogation techniques (detection of a fluorescent label on the receptor). Pertinent receptors listed in their definitions include microorganism receptors, catalytic polypeptides, enzymes, hormone receptors and opiate receptors. In both the disclosed practice of their invention and in their examples the receptor is exposed to the ligands attached to linkers whose lengths have been optimized for binding between the immobilized ligand and the free receptor. However, the optimal linker (or tether) length for binding between ligand and receptor is different for a free receptor (as disclosed in the text and examples of Fodor, et al.) and the receptor naturally embedded in its host microorganism and/or cell. Additionally, work with peptide ligands (illustrated recently by R. Hahn, E. Berger, K. Pflegerl, and A. Jungbauer "Directed Immobilization of Peptide Ligands to Accessible Pore Sites by Conjugation with a Placeholder Molecule, *Anal. Chem.* **2003**, *75*, 543-548) shows that (1) binding of macromolecules depends more upon the accessibility of the macromolecule to the ligand, and (2) the effects of ligand tether length are

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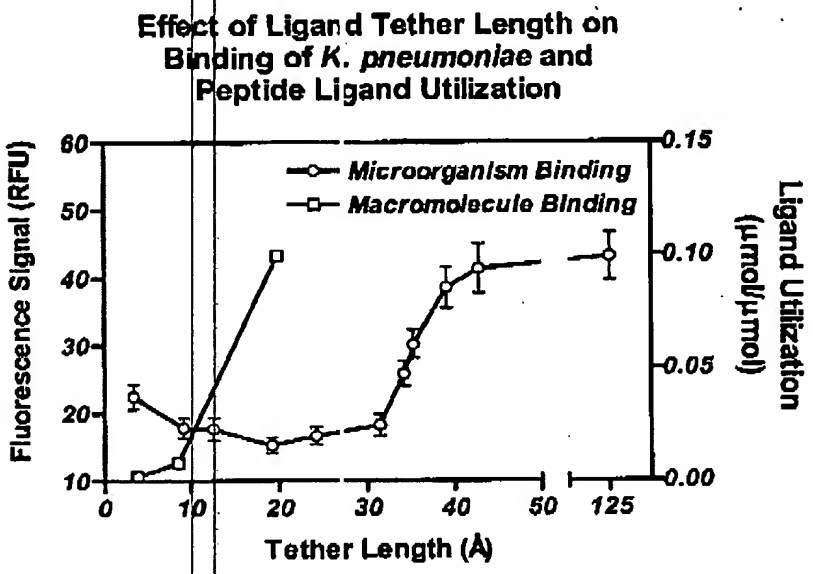
realized at much shorter lengths. The following data (shown with circles in the figure below) are provided to illustrate the complexity of the relationship between tether length and binding efficacy when intact microorganisms are involved:



This figure shows the effect of the length of the tether between a surface and a ligand (iron-containing deferoxamine) on the binding of a microorganism (*Klebsiella pneumoniae*). At shorter tether lengths (<10 Å) binding is superior to that observed at medium lengths (*ca.* 20 Å) and, as is taught in the current application, optimizes at lengths at around 40 Å; longer tether lengths affect affinity little. (These data clearly show that the efficacy of capture of the target microbe is not an easily predictable function of the tether length.) Optimal tether lengths for binding between small, non-antibody based ligands and solubilized free proteins, as disclosed in the claims of the current application, are found at lengths not much greater than six to ten Å. The data from Hahn, *et al.* (shown with squares in the figure above) confirm our disclosure and illustrate the

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predicted effect of tether length on normalized ligand utilization (μmol target captured/μmol ligand on the surface). We have not observed any improvement in binding of macromolecules (unlike microorganisms) when the tether length exceeds 20 Å; this observation is indirectly confirmed by the fact that there are few commercially available linkers/tethers that exceed 15 Å in length. As there are no obvious physiological structures on the surface of *Klebsiella* spp. to account for the differences between optimal tether lengths of the intact microorganism and its free receptor, and as our technique does not teach the optimization of the tether length for each receptor as part of its practice, and as Fodor, et al. does not teach the existence of any specific relationship that would be obvious to one skilled in the art to maximize the effectiveness of assays by adjusting the length of the tether to account for the size of the target analyte if it is a microbe, it is our position that the indication of the required minimum tether length in the application is not inherently obvious. In summary, required tether lengths depend upon the particle in which the receptor is embedded, NOT on the receptor itself or on the ligand-receptor pair.

U. S. Patent application US 2002/0187464 A1 (Klempner, et al.) is cited against the claims when the claims are interpreted as reading on methods where the ligands are antibodies (ALRs; affinity ligand reagents). Whereas lines 10-11 on page 14 of our application state, "Peptide ligands can typically be identified by affinity panning of libraries of oligopeptides and then synthesized chemically," indicating that the peptides disclosed in our disclosure are synthetic linear peptides and not immunological in origin; nor are the ligands disclosed in our

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application coupled to or the result of bacteriophage assembly (as in paragraphs 0012 [pg. 2], 0013 [pg. 2], 0018 [pg. 2], and 0022 [pg. 3] of Klempner, et al.); nor are the ligands disclosed in our application selected from a group of ALRs that have been previously bound to biological constructs (analytes) (as in paragraph 0016 on pg. 2 of Klempner, et al.). As our claims should be read to exclude antibody-derived ligands, Klempner, et al. alone does not teach the preference for ligands that are non-immunological. Furthermore, no tether is necessary for binding of microorganisms to ligands (or ALRs) associated with bacteriophage particles. Additionally, it is our opinion that the tether lengths disclosed in our application are not obvious in light of the arguments above.

14. It is noted that similar obviousness rejections to those above was presented in the parent application, and that the Applicant submitted and an Affidavit or declaration to overcome the rejections on the basis of the length of the tether between the ligand and the substrate. Affidavits or declarations, such as those submitted under 37 CFR 1.131 and 37 CFR 1.132, filed during the prosecution of the patent application do not automatically become part of the application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in the later application and include a copy of the original affidavit or declaration in the parent application.

Response: The applicant recognizes that affidavits and declarations (such as those submitted under 37 CFR 1.131 and 37 CFR 1.132) filed during the prosecution of the patent application do not automatically become part of the

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application. The applicant has provided similar material from the previously filed affidavit to address the obviousness arguments provided above.

Double Patenting

16. Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 6, 21, 23 and 27 of U.S. Patent 6,780,602. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the patent represent a species of the presently claimed invention, and would anticipate the claims of the present application is applied as prior art. Because the current claim is generic to the claims of the patent, it is rejected for obviousness type double patenting.

17. Claim 1 is provisionally rejected under the judicially created doctrine of obviousness -type double patenting as being unpatentable over claims 1, 2 and 8 of copending Application No. 10/706,542. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application read on overlapping subject matter that would have anticipated the present claim if applicable to prior art. Because the current claim is generic to the claims of the patent, it is rejected for obviousness type double patenting.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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18. Claim 1 is provisionally rejected under the judicially created doctrine of obviousness -type double patenting as being unpatentable over claims 21 of copending Application No. 10/706,542. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application read on overlapping subject matter that would have anticipated the present claim if applicable to prior art. Because the current claim is generic to the claims of the patent, it is rejected for obviousness type double patenting. It is noted that the claims of the copending application do not state the biological analyte is a virus, or that the ligand is a specific to a outer membrane protein thereof. However, such embodiments are disclosed by the specification of the copending application. See e.g., page 7, and the abstract.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response: Claim 1 of the present application was considered patentably distinct from claims 1, 2, 6, 21, 23 and 27 of U.S. Patent Application 09/999,159 (the parent patent application of U.S. Patent 6, 780,602) by the U.S. Patent and Trademark Office in a communication received by them on 14 November 2002 in which they requested an election/restriction. The patentably distinctness of claim 1 of the present application from the claims in U.S. Patent 6,780,602 was confirmed by final rejection by examiners of the U. S. Patent and Trademark Office of subsequent applications to link these claims, in which applicant claimed that the instant claim 1 traversed on the ground that the species were not patentably distinct.

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It is believed the claim is now in condition for allowance, which action is respectfully requested. Should the examiner have any questions, he is requested to call Applicants' undersigned attorney collect at (801) 521-3200.

Respectfully submitted,

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